

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

HOIBERG AS
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DANEMARK

RECEIVED
25 NOV. 2005
HOIBERG

PCT

WRITTEN OPINION
(PCT Rule 66)

Date of mailing (day/month/year)	24.11.2005
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Applicant's or agent's file reference P792PC00	REPLY DUE	within / month(s) from the above date of mailing
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International application No. PCT/DK2004/000454	International filing date (day/month/year) 25.06.2004	Priority date (day/month/year) 26.06.2003
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International Patent Classification (IPC) or both national classification and IPC C07K1/04, C07B61/00
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Applicant CARLSBERG AS

1. This written opinion is the **second** drawn up by this International Preliminary Examining Authority.
2. This opinion contains indications relating to the following items:
 - I ☒ Basis of the opinion
 - II ☐ Priority
 - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
 - IV ☐ Lack of unity of invention
 - V ☒ Reasoned statement under Rule 66.2(a)(II) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
 - VI ☐ Certain documents cited
 - VII ☐ Certain defects in the international application
 - VIII ☐ Certain observations on the international application
3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.
4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 26.10.2005

Name and mailing address of the international preliminary examining authority:	Authorized Officer
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10/561803

IAP20 Rec'd PCT/PTO 22 DEC 2005

WRITTEN OPINION

International application No. PCT/DK2004/000454

I. Basis of the opinion

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed"*):

Description, Pages

1-70 as originally filed

Claims, Pages

1-143 as originally filed

Drawings, Sheets

1/14-14/14 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

5. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

6. Additional observations, if necessary:

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V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. Statement**

Novelty (N)	Claims	1-143
Inventive step (IS)	Claims	1-143
Industrial applicability (IA)	Claims	

2. Citations and explanations**see separate sheet****BEST AVAILABLE COPY**

**WRITTEN OPINION
SEPARATE SHEET**

International application No. PCT/DK2004/000454

IAP2013/000110 22 DEC 2005

Re Item V**Reasoned statement with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement**

Reference is made to the following documents:

- D1: J. Comb. Chem. 3, 2001, pages 45-63;
D2: J. Comb. Chem. 3, 2001, pages 34-44;
D3: Chemistry - A European Journal 5(4), 1999, pages 1218-1225;
D4: Tetrahedron Lett. 44(19), 5 May 2003, pages 3835-3838.

1) D1 (see i. a. Figure 2) discloses the formation of peptide libraries ending with a polycyclic derivative prepared with the use of the Pictet-Spengler reaction, whose intermediate is known to be an N-acyliminium ion. To this respect see also Scheme 8 of the same document. In particular, scheme 8 of the present document shows an intramolecular Pictet-Spengler reaction which takes places starting from a compound falling into the wording of claims 1ff.

D2 discloses (see Scheme 5) the preparation of peptide isosters ending in a polycyclic derivative by the use of the Pictet-Spengler reaction. These isosters can immediately be used as building blocks in the preparation of libraries, and this is evident already in the title. The use of Pictet-Spengler in this reaction is, however, intermolecular.

D3 discloses the preparation of polycyclic compounds from N-terminal peptide aldehydes immobilized on a support. Though the use of those in the preparation of libraries is not alluded to in the title, it is sufficient to read the first lines of the introduction and the possibility of their use as building blocks in the preparation of libraries becomes evident to the skilled artisan. Figure 1 shows that the Pictet-Spengler reaction leading to cycles can also be intramolecular.

D4 discloses the use of the Pictet-Spengler reaction in the preparation of peptide libraries ending with polycyclic compounds. The examples provided in this disclosure refer only to intermolecular Pictet-Spengler reactions.

On the basis of the above disclosures it is concluded that claims 1-143 of the present application are deemed to lack novelty under Art. 33(2) PCT on the basis of D1 and D3. The applicant is however reminded that the structure of claim 1 ff. is also anticipated in the disclosures D2 and D4, since the definition of "nucleophile" is too generic to permit an

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SEPARATE SHEET**

International application No. PCT/DK2004/000454

assessment of what is really meant (probably the use of the N-heterocyclic atom of a tryptophane residue as nucleophile).

2) On the basis of D1-D4, the objective problem underlying the present application consists in the provision of alternative libraries and method to prepare them. There is no appreciable difference between the present application and the documents cited above. No unsuggested technical feature is evidenced, nor is any surprising effect brought to the attention of the skilled person. Therefore an inventive step under Art. 33(3) PCT cannot be recognized for claims 1-143 of the present application.

3) Claims 1-143 are endowed with industrial applicability under Art. 33(4) PCT.

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